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CLINICAL REPORT

Severe intraoperative hypertension after induction of anesthesia in a child with a neuroblastoma

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Abstract Neuroblastomas are the most common, non-central nervous system tumor of childhood. Similar to pheochromocytomas, they are derived from neural crest cells and therefore retain the potential to synthesize catecholamines. Unlike pheochromocytomas, however, perioperative issues related to blood pressure instability with hypertension are uncommon. We report details of a 3-year-old child with a neuroblastoma who developed severe hypertension and end-organ effects after induction of anesthesia. The association of such problems with neuroblastoma is reviewed and options for perioperative care presented.

Keywords Neuroblastoma · Intraoperative hypertension · Perioperative management · Clevidipine

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Introduction

A variety of factors may be responsible for hypertension during the perioperative period, including an inadequate plane of anesthesia, hypercarbia, and hypoxemia [1]. In rare circumstances, hypertension results from the paraneoplastic effects of tumors and their active chemical products [2–4]. Hypertension and other problems generally associated with excess catecholamine from pheochromocytomas are much less common with neuroblastoma. We report details of a 3-year-old child with a neuroblastoma who developed severe hypertension and end-organ effects after induction of anesthesia. The association of such problems with neuroblastoma is discussed and previous reports were reviewed.

Case report

Institutional Review Board approval is not required at the Nationwide Children's Hospital for presentation of case reports. The patient was a 3-year-old, 16-kg child who, after initial chemotherapy, presented for exploratory laparotomy, left adrenalectomy, and excision of residual tumor. Shortly after initial diagnosis, urine analysis revealed elevated concentrations of HVA (111.9 μg/mg creatinine; reference range 6–30 μg/mg creatinine), and VMA (130.7 μg/mg creatinine; reference range 5.1–16.3 μg/mg creatinine). The patient had experienced a brief period of hypertension shortly after initial diagnosis which was treated with amlodipine. The hypertension resolved and the therapy was discontinued. Current home medications included ondansetron and trimethoprim-sulfamethoxazole. The patient's mother reported that he had had one previous episode of tachycardia and hypertension after general

anesthesia for computed tomography imaging; this had resolved without intervention.

The patient was held nil per os for 6 h and then transported to the operating theater. Anesthesia was induced with propofol 40 mg (2.5 mg/kg) and neuromuscular blockade was achieved with rocuronium 12 mg (0.75 mg/kg), administered intravenously through the existing central intravenous line. After confirmation of successful endotracheal intubation, an arterial cannula was placed in the right radial artery. Immediately thereafter, the BP increased to 180/100–120 mmHg with an increase of the heart rate (HR) to 200 beats/minute. No response was noted after administration of fentanyl (2 μg/kg). After ruling out inadequate anesthesia and medication error, a clevidipine infusion was initiated at 0.5 μg/kg/min and titrated up to 2 μg/kg/min which resulted in a decrease of the BP to 140/90 mmHg. After adequate BP control, tachycardia was treated with intermittent boluses of esmolol. While hemodynamic function was improving, reduced lung compliance and oxygen saturation were noted. A chest radiograph revealed bilateral alveolar infiltrates consistent with pulmonary edema. The surgical procedure was cancelled. On arrival at the pediatric intensive care unit (PICU) while receiving continuous sedation with propofol (75–100 μg/kg/min), the HR was 130 beats/minute with BP 90–100/40–50 mmHg after discontinuation of the clevidipine infusion. Transthoracic echocardiography revealed moderate left ventricular dysfunction, which resolved on repeat examination the next day. Within 24 h, the pulmonary edema resolved, and his trachea was extubated. Analysis revealed elevated concentrations of catecholamines and their metabolites in both urine and plasma. The patient was treated for 7 days with phenoxybenzamine, with sodium loading and intravascular expansion using normal saline at 1.5–2 times the maintenance rate. Propranolol was added to treat tachycardia. The patient was returned to the operating theater for the planned surgical procedure. General anesthesia was induced with propofol (4 mg/kg) and remifentanil (2 μg/kg). Neuromuscular blockade was initiated with rocuronium (0.6 mg/kg). No significant change in the vital signs occurred with induction of anesthesia and endotracheal intubation. After induction of anesthesia, an arterial cannula was placed in the radial artery. Anesthesia was maintained with oxygen, air, sevoflurane, remifentanil, and intermittent doses of rocuronium. During surgical manipulation of the tumor, there were periods of hypertension with a systolic BP of 120 mmHg and tachycardia with a HR of 120 beats/minute. The hypertension was controlled with a clevidipine infusion at 0.5–2 μg/kg/min. After tumor excision, BP support was provided by volume administration and a phenylephrine infusion (0.5–2 μg/kg/min). The phenylephrine infusion was discontinued before he left the operating theater. After completion of the surgical procedure, the patient's trachea was extubated and he was transferred to post-anesthesia care unit (PACU) in a stable condition. On discharge from the PACU, the BP was 94/56 mmHg with a HR of 106 beats/minute. The remainder of his postoperative course was unremarkable.

Discussion

Similar to pheochromocytomas, neuroblastomas are derived from neural crest cells and therefore retain the potential to synthesize catecholamines. Although hypertension may occur early in the diagnosis, because of either catecholamine production or renal artery compression, perioperative BP issues are uncommon compared with pheochromocytomas.

As early as 1992, significant intraoperative hypertension was reported during tumor excision in a 4-month-old infant [4]. The authors went on to review the anesthetic records of 127 pediatric patients during neuroblastoma resection. Only 9 of the patients had preoperative signs and symptoms suggestive of catecholamine excess, including flushing, diaphoresis, or hypertension, even though most (81 of the 94 patients) had elevated urine or serum catecholamine levels. Intraoperative hypertension was uncommon, occurring in only two other patients in the cohort of more than 100 (incidence <3 %). Similarly, Kain et al. [3] reported intraoperative hypertension in only 3.5 % of 59 consecutive children with neuroblastoma during surgical procedures. Additional anecdotal reports of perioperative hypertension and neuroblastoma are summarized in Table 1 [4–9]. Others have reported severe hypertension in patients with neuroblastoma outside the perioperative period [10–13].

Although both pheochromocytomas and neuroblastomas produce different quantities and ratios of catecholamines including dopamine, epinephrine, and norepinephrine, the infrequent occurrence of hypertension with neuroblastoma may relate to several factors. Differences in the enzymatic capabilities of the tumors include a lack in the neuroblastoma cells of the enzyme that N-methylates norepinephrine to epinephrine; a variable concentration of the enzyme, β-hydroxylase, which converts dopamine to norepinephrine; and a relative decrease in the number of intracellular storage granules in neuroblastoma [14]. Despite these potential differences, as noted for our patient and from anecdotal reports in the literature, profound hypertension can occur at different stages during care of patients with neuroblastoma.

Although considered routine care in pheochromocytoma, routine preoperative preparation is not generally regarded as necessary for patients with neuroblastoma. The most common preoperative therapeutic agent for patients

Table 1 Previous reports of preoperative hypertension with neuroblastoma

Authors and references	Patient demographics	Symptoms	Preoperative medication	Intraoperative hemodynamics	Intraoperative medication
Haberkern et al. [4]	4-month-old, 5.4-kg infant	Preoperative hypertension (164/92 mmHg) and tachycardia. Intraoperative hypertension and tachycardia with tumor manipulation	Because of preoperative hypertension, treatment was initiated with phenoxybenzamine	During tumor manipulation, BP increased from 80/40 to 135/80 mmHg and HR increased from 120 to 140 bpm	Hypertension controlled with sodium nitroprusside
Seefelder et al. [5]	5 year-old, 14-kg girl with right adrenal neuroblastoma	Severe hypertension and tachycardia noted on initial presentation	Preoperative phenoxybenzamine and oral enalapril. Transitioned from phenoxybenzamine and enalapril to doxazosin	Severe hypertension (BP 270/150 mmHg) and tachycardia (HR 150 bpm) after induction of anesthesia and endotracheal intubation	Initial hypertension treated with hydralazine and propranolol. During tumor manipulation, BP controlled with fenoldopam (0.1–0.7 μg/kg/min) and sodium nitroprusside (0.25–2 μg/kg/min). After removal of the tumor, BP was maintained with phenylephrine (0.3 μg/kg/min) and dopamine (5 μg/kg/min)
Hernandez et al. [6]	4-month-old, 6-kg infant	Initial presentation included hypertension (BP 119/79 mmHg), tachycardia, and diaphoresis	Preoperative phenoxybenzamine followed by labetolol to treat tachycardia	Intraoperative hypertension with tumor manipulation	Intraoperative BP controlled with sodium nitroprusside (0.25 μg/kg/min), esmolol (50 μg/kg/min), and a single bolus dose of magnesium sulfate (50 mg/kg). BP support with dopamine after tumor excision
Pappas et al. [7]	33-month-old, 9.9-kg girl with large thoracoabdominal mass	Initial presentation included tachycardia (HR 120–160 bpm) and hypertension (BP 120–160/70–95 mmHg)	Intravenous labetalol, starting at 1 mg (0.1 mg/kg) and increasing every 2 h to 2, 5, 7.5, and 10 mg (1 mg/kg), repeated every 4 h for a total of 5 doses	No intraoperative hypertension noted	No vasoactive medication was required during the 12 h surgical procedure. After the second resection of residual tumor, tachycardia and hypertension continued postoperatively, requiring intermittent labetalol administration
Uchida et al. [8]	5-month-old infant	No preoperative BP issues noted	No preoperative anti-hypertensive agents required	Intraoperative hypertension noted with tumor manipulation	BP controlled with prostaglandin E_1 infusion (0.1–0.5 μg/kg/min). No hypotension noted after tumor removal
Sellden et al. [9]	4-week-old infant	Hypertensive crisis during the first weeks of life	Preoperative treatment with α-adrenergic blockade did not control BP	Intraoperative hypertension with BP up to 130 mmHg	Intraoperative BP control with adenosine (100 μg/kg/min)

BP blood pressure, *HR* heart rate, *bpm* beats per minute

with pheochromocytoma remains phenoxybenzamine, a non-competitive, long-acting, non-selective α-adrenergic antagonist. However, intraoperative hypertension may still occur during tumor manipulation despite adequate α-adrenergic blockade. Additionally, orthostatic hypotension and reflex tachycardia occur because of the non-specific blockade of presynaptic α_2-adrenergic receptors, frequently necessitating addition of β-adrenergic blockade. Most importantly, given its long duration of action, significant hypotension frequently occurs after tumor removal, which necessitates fluid administration and occasionally large doses of α-adrenergic agonists. Because of these concerns, use of alternative agents, for example prazosin has been suggested.

In summary, we report profound intraoperative hypertension after induction of anesthesia in a child with neuroblastoma. As noted for our patient and from anecdotal reports in the literature, profound hypertension can occur at different stages during the care of patients with neuroblastoma. The magnitude of the hypertension and the end-organ responses are similar to those with pheochromocytoma, albeit less frequent. Given the low incidence of such problems, routine preparation, such as is done for patients with pheochromocytoma, does not seem warranted. Intraoperative hypertension and tachycardia have been noted with tumor manipulation, thereby emphasizing the importance of invasive blood pressure monitoring and rapid access to vasoactive medications in the event that treatment of hypertension is necessary.

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